

MINIREVIEW

The G Protein Subunit Gene Families

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Receptors on cell membranes sense a variety of signals such as neurotransmitters, hormones, and light. The vast majority of such receptors are coupled to G proteins, which transduce the signal to effectors. G proteins are heterotrimers made up of an α , a β , and a γ subunit (29). The G protein subunits are now known to be encoded by families of related genes in mammalian cells (74). The sizes of these mammalian gene families vary. α subunits are encoded by 16 genes, β subunits are encoded by 5 genes, and γ subunits are encoded by 12 genes.

After the initial discovery of G proteins, most work focused on the α subunit. To identify the molecular basis for diversity in α subunit types, genes for this subunit were cloned and characterized (41). Additional interest in the α subunit genes was stimulated by the discovery of mutations in these genes associated with human disease (76). In the past few years, several genes for the β and γ subunits have also been identified and characterized (18, 19, 22, 38, 64, 73, 80). Information about these three gene families has also come from the large-scale human and mouse genome sequencing efforts. The recently completed characterization of the genomes of *Saccharomyces cerevisiae* and *Caenorhabditis elegans* allows us to compare the size and extent of diversity of the mammalian G protein subunit gene families with that of a unicellular eukaryote and a lower invertebrate (<http://www.ncbi.nlm.nih.gov/PMGifs/Genomes/yc.html> and <http://www.ncbi.nlm.nih.gov/PMGifs/Genomes/ce.html>). We focus here on some aspects of the G protein subunit genes: (i) We summarize the existent information on the structure, expression, and organization of these genes. (ii) We focus on mutations in the genes for G protein subunits that result in disease and the molecular basis for their deleterious effect on cells. (iii) We discuss the implications of the increase in diversity and size of the G protein subunit gene subfamilies with cellular complexity. Recent reviews focusing on various related aspects of G proteins are available (21, 27, 32, 62).

G Protein Subunit Function

The α subunit is a GTPase. When the receptor stimulates the G protein, the α subunit releases GDP and binds GTP. In this activated state, several α subunit types act directly on effector molecules to modulate their activity. α subunit types range in size from 39 to 52 kDa (29). Some α subunits show

specificity for effectors— α_s activates adenylate cyclases, α_i inhibits adenylate cyclases, and α_q activates phospholipase C isozymes (32). Specificity of α subunit types for receptors has also been demonstrated in a few cases (15, 31). Comparison of the amino acid sequences of 16 known mammalian α subunit types indicates that they fall into four subfamilies (74) (Table 1).

The β subunit is tightly bound to the γ subunit and is known to function only as such a complex. The $\beta\gamma$ complex modulates the activity of several effectors. The β subunit binds a variety of effectors and is therefore directly involved in the modulation of effector activity (9, 14). The five β subtypes identified so far are all approximately 36 kDa in size. They essentially fall into two subfamilies based on amino acid homology (86) (Table 2). Consistent with this grouping, β_5 has been shown to have distinct properties in comparison to β_1 – β_4 (50, 95).

Each of the 11 mammalian γ subunit types is approximately 7–8 kDa in size. The 12 C-terminal residues of one of the γ subunit types, γ_1 , has been shown to interact with a receptor (43, 44). Based on homology in this C-terminal domain and overall homology, the γ subunits have been grouped into four subfamilies (27) (Table 3). The implication from this grouping is that γ subunits that share identical C-terminal sequences interact with the same receptor while γ subunits with different C-terminal sequences interact with distinct receptors.

When the amino acid sequences of members of the α , β , and γ subunits are compared across mammalian species (<http://www.ncbi.nlm.nih.gov/Entrez/>), they show conservation approaching complete identity. This conservation of primary structure over extended periods of evolutionary history suggests that the differences among the G protein subunit types are of functional significance. The mouse α_{15} subunit type is a surprising exception to this generally high level of conservation, sharing less than 90% identity with its human homologue (89).

G Protein Subunit Gene Structure

Several of the genes for the α subunits have been characterized. Genes for α_{i1} , α_{i2} , α_{i3} , α_{t1} , α_{t11} , and α_{15} have intron–exon structures that are conserved (17, 34, 67). All of these genes possess eight exons that encode the protein product (Fig. 1A). There is no evidence for alternatively spliced products being encoded by these genes. The conservation of gene structure among the genes encoding the α_q and α_i subfamilies is consistent with the closer relationship between the α subunits in these two groups at the amino acid level (Table 1). The α_o gene, which falls within the α_i subfamily,

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TABLE 1
Identity Matrix of Mammalian G Protein α Subunits

Subfamily		α olf	α i1	α i2	α i3	α oa	α t1	α t2	α gus	α z	α q	α i1	α i4	α i5	α i2	α i3
α s	α s	77	40	40	40	42	39	40	41	37	39	40	39	35	36	36
	α olf		41	41	40	42	42	42	42	38	39	39	38	35	36	37
α i	α i1			87	93	72	67	69	67	67	50	51	51	43	42	39
	α i2				85	68	65	69	66	66	50	50	50	43	41	40
	α i3					66	61	65	62	65	50	48	48	41	39	36
	α oa						61	61	61	59	50	49	50	41	43	42
	α t1							78	75	53	52	51	48	44	41	38
	α t2								79	57	51	50	49	43	41	38
	α gust									57	51	50	50	41	41	40
	α z										49	48	48	41	41	39
α q	α q											84	76	54	41	43
	α i1												82	56	43	44
	α i4													54	42	44
	α i5														40	38
α i2	α i2															67

Note. Numbers indicate the percentage amino acid identity between subtypes calculated using the default settings of BLAST (NCBI). Boldface numbers indicate sequence comparisons between α subunits of the same subfamily. Grouping into subfamilies is based on Simon *et al.* (74). The following sequences have been used for comparison with their GenBank accession numbers given in parentheses: human α s (386743), human α olf (4097329), human α i1 (121019), human α i2 (121023), human α i3 (120996), mouse α oa (120975), human α t1 (121032), human α t2 (232151), rat α gust (121036), human α z (121005), human α q (2506475), human α i1 (3041682), human α i2 (417030), human α i3 (2494886), mouse α i4 (232137), and mouse α i5 (232138).

has a structure that is similar to the genes in the α i/ α q subfamily. However, it contains two additional exons (7A and 8A) downstream of exons 7B and 8B (81) (Fig. 1B). There is a high level of homology between the corresponding pairs of exons—7A/7B and 8A/8B. Alternatively spliced cDNAs containing either of these two pairs of exons are expressed from this gene (78). These splice products encode the α oA and α oB proteins. Since the C-terminal portion of the α subunit has been implicated in receptor interaction (32), evidence for splicing at the C terminus raised the possibility that these two α subunits, α oA and α oB, couple selectively to different receptors. Consistent with this notion, antisense DNA specific to these α subunit types, when injected into GH3 cells, selectively inhibited signaling from the muscarinic or somatostatin receptors (45). In contrast to members of the α i and α q subfamilies, the α s gene is split into 14 protein encoding exons. Several different splice products originate from this gene (42, 46) (Fig. 1B). However, this alternative splicing occurs within the first 5 exons. Variants containing different

C-terminal tails with the potential to couple to different receptors are not therefore generated. Significant differences in the properties of the α s splice products have not been shown.

The genes for the β subunits have not been as well characterized as the α subunits. The β 3 gene is made up of at least 11 exons (73; and GenBank Accession No. 1633547). The protein-encoding region spans nine exons (Fig. 1C). Analyzing the sequence information for the β 2 gene in the GenBank database (AF053356) indicates that the protein-encoding region of the β 2 gene is similarly spread over nine exons. The exon-intron structures of the two genes are strikingly conserved with reference to the encoded proteins. Comparison of the β 2 and β 3 genes with sequence data for a partially characterized β 1 gene (AL031282) indicates that the gene structure of the entire family may be completely conserved. Splice variants of the β 1– β 4 subfamily have not been detected. In contrast, a splice variant of the β 5 cDNA containing additional 5' nucleic acid sequence compared to the β 5 cDNA has been identified (85). This results in a β 5 product with an additional 42-amino-acid sequence at the N terminus (β 5L). The relationship between these cDNAs and the gene structure is unclear since the β 5 gene has not been characterized so far.

The G protein β subunits are folded into a propeller-like structure (75, 84). Each blade of this propeller is made up of a β sheet of four β strands. There is no clear correspondence between the positions of the β sheets or a recurrent Trp-Asp motif (WD repeat) and exons in the β subunit genes (Fig. 1C). There is also no clear correspondence between domains on the β subunit that are involved in interaction with effectors (9, 25, 92) and gene structure.

Several of the G protein γ subunit genes have been characterized (18, 22, 38, 64, 80; and GenBank Accession Nos. AC002076 and AC005512). The genes are split into three exons, except for the human gene for γ 5, which consists of

TABLE 2

Identity Matrix of Mammalian G Protein β Subunits

	β 2	β 3	β 4	β 5
β 1	87	80	86	51
β 2		81	88	52
β 3			78	52
β 4				53

Note. Numbers indicate the percentage amino acid identity between subtypes calculated using the default settings of BLAST P (NCBI). Grouping into subfamilies is based on homology. The following sequences have been used for comparison, with GenBank accession numbers given in parentheses: human β 1 (121008), human β 2 (121010), human β 3 (121011), mouse β 4 (121012), and human β 5 (3023845).

TABLE 3
Identity Matrix of Mammalian G Protein γ Subunits

	γ c	γ 11	γ 2	γ 3	γ 4	γ 5	γ 8	γ 10	γ 7	γ 12
γ 1	64	75	41	40	35	31	38	38	41	46
γ c		65	48	44	40	32	33	39	48	48
γ 11			42	42	40	33	40	36	44	48
γ 2				79	76	48	71	55	75	65
γ 3					68	46	57	50	63	61
γ 4						44	63	47	62	58
γ 5							46	52	51	44
γ 8								59	59	53
γ 10									52	48
γ 7										77

Note. Numbers indicate the percentage amino acid identity between subtypes calculated using the default settings of BLAST (NCBI). Grouping into subfamilies is based on the C-terminal sequences as well as overall homology (27). The following sequences have been used for comparison; their GenBank accession numbers are indicated in parentheses: human γ 1 (585181), human γ c (3023844), human γ 11 (995921), bovine γ 2 (121016), mouse γ 3 (3983451), mouse γ 4 (1730220), human γ 5 (3851089), human γ 7 (4826746), rat γ 8 (1169865), human γ 10 (995919), and bovine γ 12 (2494918). γ 13 (A1454466 & H46116) has been recently reported (note in proof).

four exons (55). An intron splits the coding region in all γ subunit genes. The position of this intron is conserved with reference to the amino acid sequence among homologous and orthologous γ subunit genes (18). As in the case of the α subunit and β subunit genes, there is no clear correspondence of secondary structure domains with exons in the γ subunit genes (Fig. 1D).

Although the gene products in Tables 1, 2, and 3 are from different mammalian species, there is evidence from the database that all 16 α subunits, 11 γ subunits, and the β subunits other than β 4 are expressed in at least two different mammals (β 4 cDNA has been isolated only from mouse). It is therefore highly likely that the genes for each of the G protein subunit gene families are conserved in all mammals.

Organization of the G Protein Subunit Genes in Mammalian Genomes

Efforts from individual laboratories combined with large-scale EST mapping programs have resulted in the identification of most G protein subunit gene loci in the mouse and/or human genomes (Table 4). Notably, four pairs of the α subunit genes—*Gnai3/Gnat2*; *Gnat1/Gnai2*; *Gna15/Gna11*; and *Gnaq/Gnai4*—have been found to be arranged as tandem duos in both the mouse and the human genomes (70, 89). The genes constituting two of these gene duos, *Gna11/Gna15* (mouse) and *GNAQ/GNA14* (human), lie in a head-to-tail arrangement (17, 70). The functional significance of this tandem organization is unclear. However, the mapping data have been used to provide a model of α subunit gene evolution (89). According to this model, genes in the α i and α q class descended from a common or independent progenitor(s) that had undergone tandem duplication. The genes for α z (*Gnaz*), α i-1 (*Gnai1*), and α oa (*Gnao*), however, do not seem to possess a tandem partner. It is hypothesized that a linked gene was lost entirely or partially (in the case of *Gnao*, which expresses products that are spliced). Alternatively, some of these genes may have evolved before the duplication event. The fewer number of exons in the α z gene in comparison to the gene encoding the α i3 subunit (Fig. 1A) does indicate that it diverged from the α i3 gene earlier in evolution than the genes for the α i1, α i2, α o, α t1, and α t2 subunits.

Most of the β and γ subunit genes have also been mapped

(1, 19, 30, 38, 64, 72, 87) (Table 4). These genes are well dispersed in both the mouse and the human genomes with the exception of a tandem pair of γ subunit genes—the *GNGT1* (γ 1) and *GNG11* (γ 11) genes (AC002076). They are in a head-to-tail orientation separated by a distance of >10 kb. In addition, the mouse γ 3 gene is organized in a head-to-head fashion with a linked gene, *Gng3lg*, of unknown function (18). This organization is conserved in the human genome (G.B.D. and N.G., unpublished results). The orientation, the close proximity of transcription initiation sites, and the expression patterns of these two genes raise the distinct possibility that shared regulatory elements are used to control their expression.

Comparison of the organization of the mammalian G protein subunit genes with their organization in *C. elegans* does not provide clear insights into the genesis of their diversity. In *C. elegans* the α subunit genes are distributed over several chromosomes with some clustering on two—chromosomes I and V (35). While one of these clusters contains a homolog of the mammalian α i subfamily, the other does not contain any such mammalian homologue.

Subunit Expression

In terms of tissue-specific expression, mammalian G protein subunit genes fall into three categories (Table 5): (i) G protein subunit genes that are expressed ubiquitously or in many tissues; (ii) a subset of genes that is expressed mainly in one tissue— β 5, γ 3, and γ 4 in the nervous system and α 15 in hematopoietic cells; and (iii) a smaller subset that is expressed in a specialized cell type—genes for α t1/ γ 1 in rod photoreceptors, genes for α t2/ γ c in cone photoreceptors, and the gene for α gust in taste buds. The reasons for specific expression of some G protein subunit genes in a particular tissue are unclear. Restricted expression of the genes for α t1/ γ 1 in rod photoreceptors is more likely due to the particular requirements of signal amplification in the rhodopsin-Gt system rather than for achieving specificity since it has been shown that Gt1 interacts more effectively with rhodopsin than Gi or Gs (12, 43).

Recent examination of α s expression in mice indicates that even though a G protein subunit may be expressed widely in mammalian organs, it may show subtle variations in expression between tissues. Studies on *Gnas1* gene knockout mice

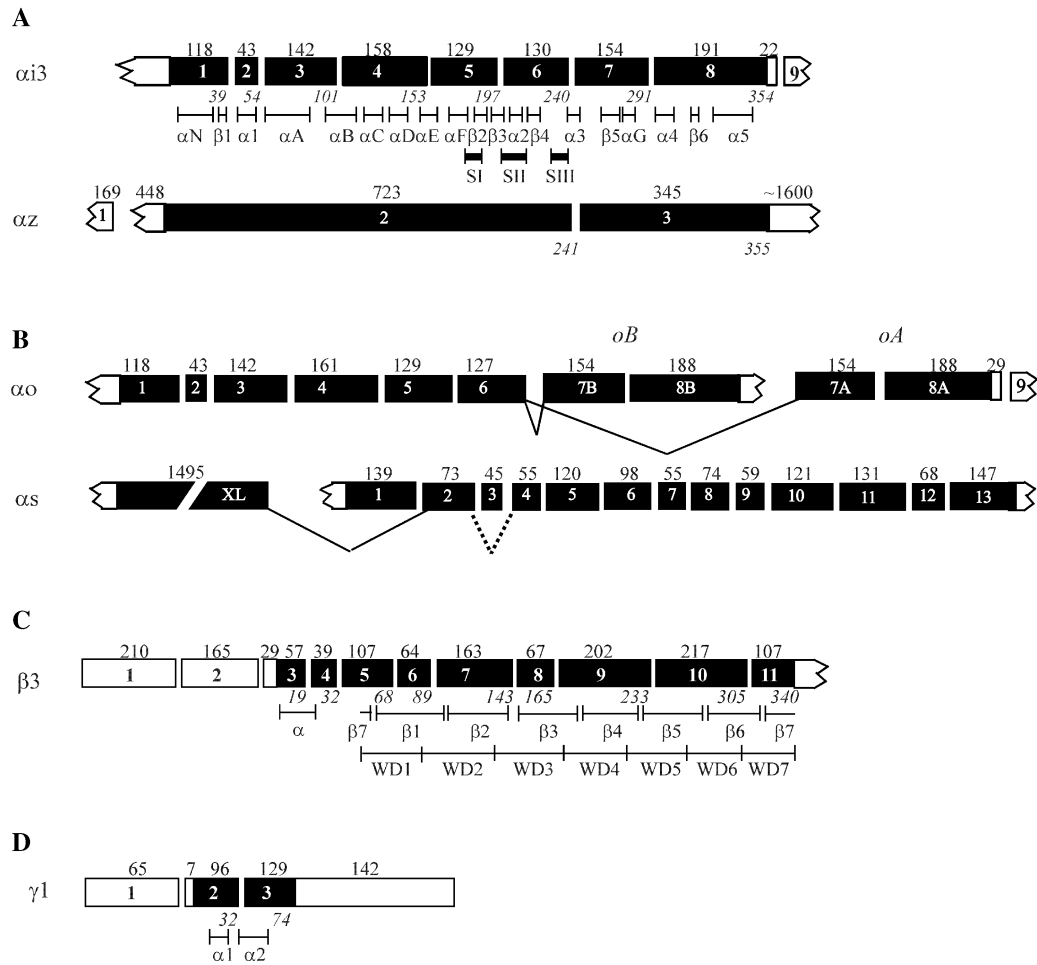


FIG. 1. Structure of G protein subunit genes. **(A)** Structure of the human genes for $\alpha i3$ (34) (AH001471) and αZ (56) (see rat αZ , U77483, U77484, and U77485). Since the α subunit types most likely have a conserved tertiary structure, the secondary structure domains from the crystallized αt protein (47) are aligned below. SI, SII, and SIII are switch regions that undergo conformational changes during nucleotide exchange. **(B)** Structure and potential splice products from the human αO (81) (AH002708) and αS (46) (AH002748) genes. The αO gene yields two splice products— $\alpha O A$ and $\alpha O B$. There are at least five αS splice products: (i) containing the XL exon instead of exon 1 (42) (ii) exon 3 spliced out with two different splice junctions; and (iii) exon 3 retained with two different splice junctions. The αZ gene is in alignment with the $\alpha i3$ gene (intron between exons 6 and 7 of *GNAI3* is conserved as the intron between exons 2 and 3 of *GNAZ*). **(C)** Structure of the human $\beta 3$ gene (1633547). **(D)** Structure of the bovine $\gamma 1$ gene (80) (S62029 and S62031). The secondary structure elements of the $\beta 1$ subunit and $\gamma 1$ subunit from the crystal structure of the complex (75) are shown at the bottom. The positions of WD repeats are from the primary structure of $\beta 2$ (23). Boxes indicate exons. Length in basepairs is shown above the boxes, and length in amino acids is shown below the boxes. Filled boxes indicate protein encoding regions. Jagged edges indicate either that the entire exon is not shown or that the exon is not fully characterized. Alternative splicing is indicated by solid or dashed lines.

indicate that this gene is paternally imprinted in a tissue-specific manner (94). The implications of this finding are discussed in the next section. Analysis of the locus in mice that contains the *Gnas1* gene indicates that three genes are clustered in this region—*Gnas1*, *Gnasxl*, and *Nesp* (66). Notably, they are part of a single transcription unit. The products of the *Gnasxl* and *Nesp* genes are spliced onto exon 2 of *Gnas1*. *Gnasxl* is maternally imprinted, and *Nesp* is paternally imprinted. These two genes show patterns of methylation consistent with this imprinting. However, *Gnas1* is not methylated, and it is hypothesized that in tissues where *Gnasxl* is maternally imprinted the expressed paternal allele competes for transcription factors with the paternal allele of *Gnas1* and silences it.

Diseases Associated with Defects in G Protein Subunits

The alterations in G protein α subunits that lead to human disease can be (i) modifications introduced by extraneous

agents, (ii) somatic mutations, and (iii) heritable mutations (Table 4).

(i) Cholera toxin and pertussis toxin are two toxins that ADP ribosylate certain G protein α subunits and profoundly alter their function. Cholera toxin from *Vibrio cholerae* is an ADP ribosyltransferase that transfers the ADP group from NAD to αs (59). The target residue is Arg 201 in αs . This residue is involved in stabilizing the transition state during the hydrolysis of GTP to GDP. The presence of a bulky ADP ribose group at this position thus prevents GTP hydrolysis. The resultant constitutive function leads to high cAMP levels and extrusion of chloride ions and water from intestinal cells. Pertussis toxin from *Bordetella pertussis* ADP ribosylates a Cys residue at the C terminus of several G protein α subunits (59). Since the C terminus is involved in interaction with the receptor, the attachment of an ADP ribose moiety prevents receptor

TABLE 4
The Mammalian G Protein Subunit Genes

Gene symbol	Encoded proteins	Human genome location	Potential disease association
<i>GNAS1</i>	α S-S-A, α S-S-B, α S-L-A, α S-L-B, α S-XL	20p13 (Hs. 113368) ^a (79)	Pseudohypoparathyroidism, McCune–Albright syndrome (76)
<i>GNAL</i>	α olf	18p (Hs. 154145) (89)	
<i>GNAI1</i>	α i1	7q21 (Hs. 203862) (89)	
<i>GNAI2</i>	α i2	3p21 ^b (Hs. 77269) (89)	Ovarian and adrenocortical tumors (21)
<i>GNAI3</i>	α i3	1p13 ^b (Hs. 73799) (89)	
<i>GNAO</i>	α oA, α oB	16 (89)	
<i>GNAT1</i>	α t1	3p21 ^b (Hs. 51147) (89)	Nougaret form of congenital stationary night blindness (20)
<i>GNAT2</i>	α t2	1p13 ^b (Hs. 36973) (89)	
<i>GNAG</i>	α gust	ND ^c	
<i>GNAZ</i>	α z	22q11 (Hs. 92002) (89)	
<i>GNAQ</i>	α q	9q21 (Hs. 180950)	
<i>GNA11</i>	α 11	19p13 ^b (Hs. 1686) (89)	
<i>GNA12</i>	α 12	7p ^d (Hs. 73797) (89)	
<i>GNA13</i>	α 13	17q22–q24 ^d (Hs. 1666) (89)	
<i>GNA14</i>	α 14	9q21 ^b (70)	
<i>GNA15</i>	α 15	19p13 ^b (Hs. 73797) (89)	
<i>GNB1</i>	β 1	1p36 (Hs. 215595)	
<i>GNB2</i>	β 2	7q22 (Hs. 91299) (30)	
<i>GNB3</i>	β 3	12p13 (Hs. 71642)	Hypertension (73)
<i>GNB4</i>	β 4	ND	
<i>GNB5</i>	β 5, β 5L	15 (Hs. 155090)	
<i>GNGT1</i>	γ 1	7q21.3, 7q31–32 ^{b,e} (Hs. 73112) (72)	
<i>GNGT2</i>	γ Cone	17q21 (64)	
<i>GNG11</i>	γ 11	7q31–32 ^b (Hs. 83381)	
<i>GNG2</i>	γ 2	10q ^d (19)	
<i>GNG3</i>	γ 3	11 (Hs. 179915)	
<i>GNG4</i>	γ 4	1 (Hs. 32976)	
<i>GNG5</i>	γ 5	1p22 (Hs. 5322) (1)	
<i>GNG7</i>	γ 7	19p or 12q ^d (Hs. 127828) (87)	
<i>GNG8</i>	γ 8	19q ^d (19)	
<i>GNG10</i>	γ 10	9q ^d , 9, and 15 ^f (Hs. 79126) (19)	
<i>GNG12</i>	γ 12	2p ^d (19)	

^a Unigene (<http://www.ncbi.nlm.nih.gov/UniGene/>) database accession number.

^b Indicates colocalization with another G protein subunit gene.

^c Locus not determined.

^d Loci predicted based upon mouse mapping data.

^e There is a discrepancy between the data in the publication and those from the database.

^f Two loci have been identified.

activation of the G protein. Both cholera and pertussis toxins have been used widely in experiments to perturb signaling mediated by susceptible G proteins or to label α subunits with a radioactive ADP ribose.

(ii) Not surprisingly, mutations that alter Arg201 in α S lead to disease. Some adenomas of the thyroid and pituitary glands contain substitutions at this position of α S (21). The mutant α S is incapable of hydrolyzing GTP and is constitutively active. This constitutive activity is presumably at the basis of the hyperproliferation. McCune–Albright syndrome is characterized by a variety of abnormalities and is associated with mutations at the same position on α S (88). These mutations are, however, somatic. Their effects depend on (a) when they arise during development—late in the case of adenomas and early in the case of McCune–Albright syndrome and (b) where they occur—the effect of the mutant is dependent on the signaling pathways active in the cell type where it is expressed.

(iii) Pseudohypoparathyroidism Type I is a disease that results from a defective α S (11, 51). It is the best characterized and most convincing example of a heritable disorder resulting from

mutations in the gene for a G protein subunit. Affected individuals are heterozygous for α S mutations and have shortened fingers, toes, and stature (Albright hereditary osteodystrophy (AHO)). Some do not respond to parathyroid hormone while retaining response to other hormones such as vasopressin. This variation in the phenotype of individuals despite genotypic equivalence was a puzzle for many years. Extensive analysis of the pattern of inheritance of these phenotypes indicated that the α S gene was paternally imprinted (16). The analysis of mice with their α S gene knocked out provided elegant support for this notion and also showed that the imprinting of the α S gene was conserved across mammalian species (94). Knockout mice that were heterozygous for the defective allele of *Gnas* showed the more extreme disease phenotype—resistance to parathyroid hormone—when the mutant allele was inherited from the mother. Furthermore, the differential imprinting was observed between tissues in the kidney. This may explain the variation in response to hormones among heterozygous individuals.

Considering the central role that the G protein $\beta\gamma$ complex plays in signaling, it would be expected that mutations in the

TABLE 5

Tissue Distribution of α , β , and γ Subunits

	Tissue distribution
α s	Ubiquitous ^a (8, 48)
α olf	Olfactory neuroepithelium, low levels in brain (5, 37)
α i1	Several (8, 37)
α i2	Several (8, 37)
α i3	Several (37, 48)
α o	Predominantly expressed in brain, other tissues (3, 8, 37)
α t1	Retinal rod cells (49)
α t2	Retinal cone cells (49)
α gust	Taste buds (57)
α z	Predominantly expressed in brain, other tissues (24)
α q	Ubiquitous (90)
α 11	Several (90)
α 12	Ubiquitous (77)
α 13	Ubiquitous (77)
α 14	Several (90)
α 15	Tissues of hematopoietic lineage (90)
β 1	Ubiquitous (6, 23, 48, 53)
β 2	Several (6, 23, 53)
β 3	Several (6, 52, 53)
β 4	Several (6, 53, 83)
β 5	Brain (6, 53, 86)
γ 1	Retinal rod cells (65)
γ c	Retinal cone cells (64)
γ 11	Several, undetectable in brain (68)
γ 2	Predominantly expressed in brain, other tissues (2, 6, 26)
γ 3	Abundant in brain, low levels in testis (28)
γ 4	Brain, other tissues ^b (6, 39, 68)
γ 5	Ubiquitous (2, 6, 18)
γ 7	Predominantly expressed in brain (striatum), other tissues (6, 10, 87)
γ 8	Olfactory neuroepithelium, lower levels in brain (6, 71)
γ 10	Ubiquitous (6, 68)
γ 12	Ubiquitous (6, 58)

^a For the purposes of this table, "ubiquitous" is defined as being present in all samples, with at least 10 tissues examined.

^b There is a discrepancy between the data presented in these papers.

β and γ subunit genes too will lead to disease. So far, evidence for such mutations is limited. A mutation in the β 3 subunit gene has been shown to be associated with hypertension (73). Other evidence, however, has indicated a lack of association between the mutation in the β 3 gene and disease (7, 40). It is possible that many mutations in G protein subunits prove to be lethal because of their central role in mammalian physiology. As a result of the characterization of mammalian genomes, wider searches for mutant genes are now possible. It is likely that such searches will yield additional mutations in the genes for G protein subunits that are at the basis of disease.

One of the aims of gene mapping is to identify linkage to disease loci. The map positions of several G protein subunit genes in mice lie close to mutations that have deleterious effects on the animals (Mouse Genome Database, The Jackson Laboratory; <http://www.informatics.jax.org/>). It is unclear, however, whether these mutations lie within one of the G protein subunit genes.

Subunit Diversity

At least 20 α subunits are expressed in mammalian cells when splice variants are included. As mentioned before, they

can be grouped into four subfamilies as in Table 1. For the most part, the relationships among members in a subfamily are not functional and are likely evolutionary. For instance, α t1 activates cGMP phosphodiesterase, α o modulates the Ca^{2+} channel function, and the α i subtypes inhibit adenylyl cyclase although they all fall within the same subfamily (60). Each subfamily of α subtypes has more than one member (Table 1). The reasons for this pattern of diversity can be inferred from the nature of G protein α subunit diversity in lower eukaryotes—the unicellular yeast *S. cerevisiae* and the multicellular nematode *C. elegans*. The genomes of both these organisms have been sequenced. The yeast genome contains the genes for two α subunit types (M15867 and U18778). These yeast α subunits are most related to the α i subfamily in mammals. *C. elegans* has 20 α subunit genes and 4 gene products, which are homologous to one each of the mammalian subfamilies— α s, α i, α q, and α 12 (35). The remaining 16 *C. elegans* α subunit genes cannot be grouped with any of the mammalian α subunit gene subfamilies. Most of these 16 genes are expressed in chemosensory neurons (35). It is most likely that *C. elegans* α subunits that are not homologous to mammalian α subunits are involved in chemosensation or in the development of chemosensory neurons. The presence in *C. elegans* of only a single member belonging to each of the four mammalian subunit subfamilies contrasts with the existence of several members of each α subunit subfamily in mammals. The expansion of a few distinct α subunit genes into subfamilies is most likely specific to organisms that possess a variety of cell types organized into organs of specialized function. Expansion in the case of *C. elegans* is restricted to the α subunits involved in chemosensation. A possible reason for the expansion of subfamilies in mammals is that various cell types and organs with specific functions require distinct signal transduction pathways. The pattern of diversity seen in the case of the genes for the G protein β and γ subunits and receptors further supports the notion that the expansion of subfamilies in signal transducing proteins is correlated with increasing complexity of cellular organization.

While mammals have five β subunit genes that fall into two classes, β 1– β 4 and β 5, yeast has one β subunit gene, STE4 (M23982). The yeast β subunit shows the same level of relatedness to the mammalian β 1 and β 5 subfamilies. *C. elegans* has two β subunit genes that fall separately into the β 1 and β 5 mammalian classes (http://www.sanger.ac.uk/Projects/C_elegans). The genes for the 11 γ subunit types in mammalian cells fall into three or four subfamilies (27) (Table 3). Yeast has one γ subunit gene, STE18 (M23983), whose product shows a very low level of homology to mammalian γ subunits. The two γ subunit genes in *C. elegans* do not easily fall within the mammalian subfamilies (http://www.sanger.ac.uk/Projects/C_elegans).

The increase in size of subfamilies of G protein subunit genes in mammals compared to yeast or *C. elegans* is also seen among the genes for receptors. Mammalian genomes contain families of genes encoding receptors that sense the same neurotransmitter or hormone. For example, there are 5 muscarinic acetylcholine receptors, 5 dopamine receptors, at least 13 5-HT receptors, and 3 each of the α 1, α 2, and β adrenergic receptors (<http://www.gcrdb.uthscsa.edu>). In contrast, a similar level of diversity within subfamilies of genes for neurotransmitters or peptide receptors is not seen in the *C. elegans* genome (4). One prediction is that when the functions of *C. elegans* receptors are identified, families of sub-

types will be virtually absent. The presence in mammals of subfamilies of genes for receptors is consistent with the existence of subfamilies of genes for G protein subunit types. G proteins containing different subunit types may discriminate between subtypes of receptors that detect the same signal.

It is notable that the mammalian G protein α and γ subunit genes are much more diverse than the β subunit genes (Tables 1 and 3 compared to Table 2). This may be a reflection of the extent of functional diversity at the level of the encoded proteins. Both the α and the γ subunits have been shown to contact receptors specifically (15, 33, 43, 44, 69). Since the seven transmembrane receptor family is large and extremely diverse, variety in G protein α and γ subunit types may allow for specificity in receptor–G protein coupling. Diversity in α subunit types also contributes toward specificity for effectors. For example, α_q activates phospholipase C- β and α_s activates adenylyl cyclases (32). Although the β subunits have also been shown to interact with effectors, evidence for specificity between β subunit types and effectors is limited (13, 25, 54, 92, 93). Thus one explanation for the presence of more diverse α and γ subunits compared to the β subunits is diversity of function. The effect of knocking out certain α subunit types in mice does support this notion. Mice carrying null alleles of the α_o , α_{13} , and α_q genes show distinctive phenotypes (36, 61, 63, 82). However, the effect of knocking out other G protein α subunits in mice does not entirely support a simple relationship between gene diversity and functional specialization. Knockouts of the α_{i1} , α_{i3} , α_{i11} , α_{14} , and α_{15} genes, for instance, do not show any obvious defects (62). Although it is still possible that subtle defects in these mice are yet to be identified, these results are consistent with earlier indications from reconstitution experiments that some G protein α subunit types are capable of interacting with diverse receptors (31). Analysis of particular signaling pathways in mutant mice also supports a certain level of redundancy. For instance, Ca^{2+} release, which is mediated by members of the α_q subfamily, was not affected in cells that were mutant for α_q , α_{11} , or α_{14} , although these were the three members of the α_q subfamily expressed in these cells (91). It may be that the diversity of α and γ subtypes in comparison to the β subunits can provide selectivity in some cases while in other cases the subunits present multiple partners for interaction with the same receptor—the first and most important step in the activation of a signaling pathway. This built-in redundancy could be a mechanism that allows a signaling pathway to continue functioning in the presence of a defective subunit type.

Note added in proof. The identification of a novel γ subunit gene (Huang, L., et al. (1999) *Nat. Neurosci.* **2**, 1055–1062; and AL031033) increases the number of known members of this mammalian gene family to 12.

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